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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,137	04/25/2005	Parveen Bhatarah	1581.1120000/RWE/FRC	1688

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EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
01/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,137	BHATARAH ET AL.	
	Examiner	Art Unit	
	Jody L. Karol	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-80 and 82-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-80 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of applicant's Amendment/Remarks filed 7/24/2008. Claims 81 and 99-106 have been cancelled. Claims 1-76 were previously cancelled. Thus, claims 77-80 and 82-98 are currently pending and examined on the merits herein. Prior art is applied in so much as it reads on the elected species, budesonide.

WITHDRAWN REJECTIONS

1. Applicant's cancellation of claims 104-105 renders the rejection of these claims under 35 U.S.C. 102(b) as anticipated by Karlsson et al. (WO 99/25359) moot. Thus, said rejection has been withdrawn.

MAINTAINED REJECTIONS

2. The following rejections have been maintained from the previous Office Action dated 3/24/2008:

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 77-80, and 82-98 rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al. (US 6,187,765 B1).

The instant claims are directed to methods for preparing sterile pharmaceutical compositions of the steroid, budesonide, comprising dissolving the non-sterile steroid in a solvent to yield a solution of the steroid; filtering the solution to yield a sterile solution; combining the sterile solution with sterile water to form a suspension; optionally removing all or part of the solvent; treating the suspension to obtain a particle size

distribution having a mass median diameter less than 10 μm; under sterile conditions combining said suspension with a pharmaceutically acceptable carrier to yield a sterile composition; and storing said composition in a sterile container.

Harris et al. teaches aqueous suspensions of water-insoluble pharmaceutical substance intended for inhalation therapy (see column 1, lines 12-15). Harris further teaches in Example 1, a method of preparing a sterile suspension of a steroid, mometasone furoate, comprising dissolving said steroid in acetone, a class 3 solvent as claimed in the instant claim 83; filtering said solution through a sterilizing filter, such as a filtration medium having pore sizes not exceeding 0.2 μm in diameter, as claimed in the instant claims 89 and 96, into a sterile vessel; heating said sterile solution to about 45-50 °C and slowly adding sterile purified water over 15 min.; while maintaining the temperature and more of the sterile water and stir for 30 min.; continuing to maintain the temperature and stir for another 30 min. during which a precipitate forms; slowly adding more water and stirring for 60 min. at the elevated temperature; stirring at 60 min. at the elevated temperature; cooling the mixture to ambient temperature while stirring; filtering said precipitate and washing with water; and drying under vacuum to yield dry sterile mometasone furoate (see column 6, lines 25-62). The sterile mometasone furoate is then added to a sterile carrier solution comprising polysorbate (a surfactant) as claimed in the instant claim 90, to form a suspension; said suspension is passed through a Microfluidizer to yield a suspension with a median particle size of 1.24 as claimed in the instant claims 91 and 97 (see column 7, lines 65-68); and the sterile suspension is

transferred to sterile containers for use in a nebulizer (i.e. an ampoule as claimed in the instant claim 93) (see column 6, line 64 to column 7, line 36).

Harris et al. does not teach a method of preparing a sterile suspension of steroid where the steps are in the same order as claimed. For example, Harris et al. teaches the sterile suspension is combined with a carrier before the suspension is treated to obtain the desired particle size, which is opposite to what is claimed. However, it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. *Ex Parte Rubin*, 128 USPQ 440 (Bd. App. 1959). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946).

Harris et al. additionally teaches extra steps, such as isolating and drying the steroid. However, the term "comprising" is interpreted as broad and open, and the extra steps taught by Harris et al. are not excluded by the claim language. Furthermore, the extra step of isolating the product is not essential because it does not materially affect the end product.

Harris et al. also does not teach a method for preparing a sterile suspension of steroid wherein the steroid is budesonide. However, Harris et al. does teach that aqueous suspensions of drug particles for nebulization are known, and mentions budesonide as a commercially available product (see column 2, lines 5-12). Harris et al. also teaches that formulations that are to be inhaled must be free of pathogenic organisms, and thus be prepared and handled under sterile conditions (see column 3, lines 7-10). It would have been obvious to one of ordinary skill in the art to substitute

budesonide for mometasone furoate as the steroid in the method taught by Harris et al., to produce a sterile suspension of budesonide. One of ordinary skill in the art would have been motivated to do so in order to produce an inhalable formulation of budesonide free of any potential pathogenic organisms.

In regards to the instant claims 78-79, wherein the budesonide steroid is a powder or micronized power, Harris et al. does not explicitly teach using a powder steroid, or a micronized powder sterile to prepare the sterile suspensions. However, it would have been obvious to one of ordinary skill in the art at the time of invention to use a powder or micronized powder of the steroid to prepare the sterile suspensions because powders and micronized powders have an increase surface area. One of ordinary skill in the art would have been motivated to increase the surface area of the steroid to increase the rate at which the steroid dissolves in the solvent.

In regards to claims 82, 84, and 95, Harris et al. does not teach dissolving the steroid in alcohol or a class 2 solvent. Harris et al. teaches dissolving the steroid in acetone (as described *supra*). However, it is been held that the selection of a known material based on its suitability for its intended use supported a *prima facie* case of obviousness determination in *Sinclair & Carroll Co. V. Interchemical Corp.*, 325, US 327, 65 USPQ 297 (1945). Accordingly, since alcohol and class 2 solvents are known solvents, it would have been obvious to one or ordinary skill in the art at the time of the invention to select an appropriate solvent to dissolve the steroid.

In regards to the instant claim 85-86, the boiling point of acetone is 56.5°C. Harris et al. teaches dissolving the steroid at 45-50°C which is significantly overlaps with

the range as claimed in the instant claim 85. Harris et al. does not teach adding the steroid to the solvent wherein the solvent is at reflux. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to add the steroid to the solvent at reflux. One of ordinary skill in the art would have been motivated to do so to increase the rate at which the steroid dissolves in said solvent.

In regards to claims 87, Harris et al. does not teach removing the solvent under reduced pressure. Acetone (the solvent taught by Harris et al.) will evaporate on its own at room temperature to a certain extent. Heating any solvent or reducing the pressure any solvent is kept at, will increases the rate at which the solvent evaporates. Harris et al. heats the acetone (see column 6, lines 37-40). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to remove the solvent under reduce pressure. One of ordinary skill in the art would have been motivated to do so to increase the rate of solvent removal.

In regards to the instant claims 92 and 98, Harris et al. does not explicitly teach steroid particles in the suspension having a mass median diameter in the range of 2-3 μm. However, Hara et al. does teach that the preferred average particle size for inhaled particles is 0.5 to 5 μm (see column 1, lines 27-43 and column 2, lines 65-67). Furthermore, Harris et al. claims suspensions where the particle size is less than 5 μm, which significantly overlaps with range as claimed (see column 10, claim 14), and teaches suspensions where the median particle size is 1.24 μm. In this case, where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 UPSQ 90 (CCPA 1976).

Furthermore, while the references do not explicitly teach the claimed particle size range, it is the Examiner's opinion that the determination of optimal or workable particle size range by routine experimentation is obvious absent showing of criticality of the claimed particle size range. One having ordinary skill in the art would have been motivated to do this to obtain an optimal particle size for inhaled steroids.

Therefore, the invention as a whole would have been *prima facie* obvious to one skilled in the art at the time it was made.

Response to Arguments

Applicant's arguments filed 7/24/2008 have been fully considered but they are not persuasive.

Applicant argues that that the claimed one-step process is not obvious over the two-step process taught by Harris et al., which includes an isolation step, and that Harris et al. does not provide a reason why one of ordinary skill in the art would use a single phase method. In response, it is respectfully submitted that the isolation of the steroid is a design choice and not an essential step because it does not materially affect the end product. Solid products are often isolated because they are easier to transport than the suspended products. However, when the solid product is to be immediately processed into the final suspended product for use in a nebulizer, it would be obvious to the ordinary artisan to leave the steroid product in the water-based suspension for the further processing steps.

Applicant further argues that Harris et al. does not provide a reason why the one would treat suspension of (iii) or (iv) to reduced its particle size. It is respectfully submitted that Harris et al. teach reducing the particle size of the re-suspended steroid in water and a pharmaceutically carrier. As stated above, the addition of the pharmaceutically carrier before or after reducing the particle size is not considered to be a patentable modification and the isolation step is not viewed as an essential step. Thus, the processing of the re-suspended steroid is considered to meet this limitation.

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

Conclusion

All claims have been rejected; no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617